REMARKS

Claims 17-25, 27-29, and 31-33 are pending. Claims 17-29 were rejected under 35 U.S.C. §112, second paragraph. After entry of the claim amendments, all rejections based on indefiniteness should be obviated. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is in order and is respectfully requested.

Claim 27 was rejected under 35 U.S.C. §102(a) in light of Bolte. This rejection is respectfully traversed. Regardless of whether R^{901} is a protective group, the disclosure of Bolte is insufficient to form an anticipatory disclosure. Bolte provides the structural formula of a compound, but no way to make the compound. Making such a compound is not a routine matter to a skilled worker. Consequently, the failure to disclose a method of making the compound fails to place the invention in the hands of one of skill in the art. Courts have held such disclosures are not anticipatory, see, for example, In re Hoeksema, 158 USPQ 596 (CCPA 1968). Because Bolte is not an enabling disclosure for the disclosed compound, the rejection under 35 U.S.C. §102(a) is improper and should be withdrawn.

Claims 27 and 28 were rejected under 35 U.S.C. §103(a) over Bolte in view of Greene. This rejection is respectfully traversed. For the reasons set forth above, Bolte does not set forth an enabling disclosure of the compound it depicts. Greene fails to remedy this deficiency of disclosure. Even assuming, *arguendo*, that Greene discloses groups claimed in the present invention, the failure of Bolte to disclose the basic formula renders Greene irrelevant. Accordingly, the rejection under 35 U.S.C. §103(a) is improper and should be withdrawn.

Claims 17-25 and 31-33 were rejected under 35 U.S.C. §103(a) over Lash, Reggelin I, Reggelin II, and Bolte in view of Greene. Because the references, singly or in combination, fail to disclose or fairly suggest the presently-claimed compound, the rejection is respectfully traversed. Specific shortcomings of each reference are set forth below.

Lash describes a non-stereoselective method of synthesis, in which the pyrrolidine compounds 3a-m are intermediates. Lash does not set forth

Claims 17-33 were rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The presently-amended claims are supported by the terms of the disclosure at, *inter alia*, Example 1, pages 28-32. Therefore, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn. Reconsideration of all pending claims is in order and is respectfully requested.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #147/49227).

Respectfully submitted,

May 14, 2002

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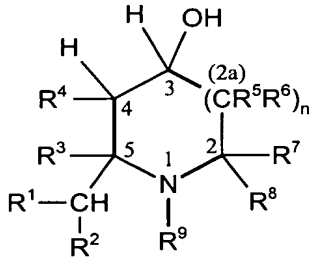
VERSION WITH MARKINGS TO SHOW CHANGES MADE

17. (Amended) A process for stereochemically controlled production of a compound corresponding to formula Ia':



Ia'

wherein the R^1R^2CH group in the 5-position of the cyclic parent structure and the hydroxy group in the 3-position of the cyclic parent structure are each in the trans position relative to each other and wherein the substituent R^4 in the 4-position and the hydroxy group in the 3-position of the cyclic parent structure are each in the cis position relative to each other, and wherein

n is 0 or 1,

R^1 is hydrogen; [C_1-C_6-alkyl; or phenyl-C_1-C_6-alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy, and]

R^2 is hydrogen;[, or]

[R^1 and R^2 together are a double-bonded methylene group which may be substituted by C_1-C_5-alkyl or by phenyl-C_1-C_5-alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

R^3 is hydrogen, and

R^4 is hydrogen[;] or lower alkyl[; or phenyl-lower alkyl optionally substituted one or more times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy], or

R^3 and R^4 also together are a [C_2-alkylene chain; or a] C_3-C_6-alkylene chain optionally containing 1 to 3 double bonds[, which may be bridged by C_1-C_2-alkylene which is optionally substituted one or two

times by lower alkyl,] or together form the 7, 7-dimethylbicyclo[3.1.1] heptyl-system

R^5 is hydrogen[;] or lower alkyl[; hydroxy; lower alkoxy; phenyl-lower alkoxy or phenyl-lower alkyl each of which may be optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy], and

R^6 is hydrogen, and

R^7 is hydrogen, and

R^8 is hydrogen;

[cyano;]

[carboxy optionally esterified with cycloaliphatic or straight-chain or branched aliphatic C_1-C_6-alcohols optionally containing one to three double bonds, and optionally substituted one to three times by halogen or lower alkoxy, or alternatively esterified with phenyl-lower alcohols optionally substituted in the phenyl ring one to three times by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[carbonylamino optionally substituted at the nitrogen once by C_3-C_8-cycloalkyl lower alkanoyl or straight-chain or branched aliphatic C_1-C_6-alkanoyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or optionally substituted at the nitrogen once by phenyl-lower alkanoyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy, or optionally substituted at the nitrogen one or two times by C_3-C_8-cycloalkyl-lower alkyl or straight-chain or branched aliphatic C_1-C_6-alkyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or by phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[carbonylamino substituted at the nitrogen with a suitable amino protecting group;]

a monocyclic or bicyclic ring system selected from the group consisting of cyclopropyl, cyclopentyl cyclohexyl, phenyl, p-bromophenyl and 3-indolyl; [with 3 to 10 ring carbon atoms which is optionally unsaturated one to four times, the ring carbon atoms of said ring system optionally being replaced one to three times by nitrogen, oxygen and/or sulfur and which ring system may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, hydroxy, halogen or by a lower

alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system;]

lower alkyl; phenyl-lower alkyl or lower-alkoxy lower alkyl [a straight-chain or branched C_1-C_{12}-alkyl group optionally containing one to three double bonds, which may optionally be substituted one to three times by]

[halogen,]

[hydroxy,]

[lower alkoxy,]

[carboxy optionally esterified with cycloaliphatic or straight-chain or branched aliphatic C_1-C_6-alcohols, which optionally contain one to three double bonds, and which are optionally substituted one to three times by halogen or lower alkoxy,]

[carboxy esterified with phenyl-lower alcohols optionally substituted in the phenyl ring one to three times by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[cyano,]

[mercapto,]

[lower alkylthio,]

[amino,]

[lower alkylamino,]

[carbonylamino optionally substituted once at the nitrogen by C_3-C_8-cycloalkyl-lower alkanoyl or straight-chain or branched aliphatic C_1-C_6-alkanoyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or optionally substituted once at the nitrogen by phenyl-lower alkanoyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

[carbonylamino substituted once or twice at the nitrogen by C_3-C_8-cycloalkyl-lower alkyl or straight-chain or branched aliphatic C_1-C_6-alkyl, which are each optionally substituted one to three times by halogen or lower alkoxy, or by phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

[carbonylamino substituted at the nitrogen with a suitable amino protecting group,]

[a monocyclic or bicyclic ring system with 3 to 10 ring carbon atoms which is optionally unsaturated one to four times, the ring carbon atoms of which may be replaced one to three times by nitrogen, oxygen and/or sulfur and which ring system may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system, or]

[R^5 and R^8 also, together with the carbon atoms to which they are bonded, may form a monocyclic or bicyclic ring system with 5 to 10 ring carbon atoms which optionally contains 1 to 3 double bonds, wherein carbon atoms not bearing the substituents R^5 or R^8 optionally may be replaced one to three times independently by sulfur, oxygen or nitrogen, and which optionally may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system], or

R^6 and R^7 also together may form a bond, and

R^5 and R^8, together with the carbon atoms to which they are bonded, may form an aromatic C_6-ring system [which may be fused with 2 to 4 further carbon atoms to form a bicyclic ring system having a total of 3 to 5 double bonds which contains a total of 8 to 10 ring carbon atoms, wherein the carbon atoms of this C_6- to C_{10}-ring system which do not bear the substituents R^5 or R^8 may be replaced one to three times independently by sulfur, oxygen or nitrogen, and wherein this C_6- to C_{10}-ring system may optionally be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system],

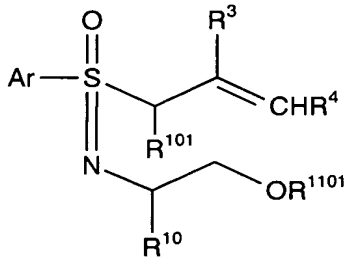
R^9 is hydrogen; lower alkyl; phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy; or an amino protecting group, or

R^8 and R^9 also together may form a C_3-C_4-alkylene chain,

or an acid addition salt thereof, wherein any reactive groups which may be present in said compound of Formula Ia' may be blocked by suitable protecting groups,

said process comprising the steps of:

a) reacting a compound corresponding to formula II:



II

wherein

R^3 and R^4 have the above meanings,

R^{101} has the meaning given above for R^1 [with the exception of an optionally substituted methylene group,]

Ar represents phenyl optionally substituted one to three times by lower alkyl,

R^{10} is lower alkyl, or phenyl optionally substituted once in the phenyl ring by lower alkyl or by hydroxy protected with a suitable protecting group, or phenyl-lower alkyl optionally substituted once in the phenyl ring by lower alkyl, and

R^{1101} stands for a silyl protecting group,

successively with

(i) a base [suitable] for the deprotonation thereof,

(ii) an organometallic reagent corresponding to the formula VII:

$$XM^2(OR^{12})_3 \qquad \text{VII}$$

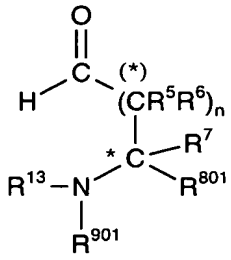
wherein

X is halogen,

M^2 is a tetravalent transition metal, and

R^{12} is lower alkyl, phenyl or phenyl-lower alkyl, and

(iii) a stereoisomer of a compound of the general formula VIII:



VIII

wherein

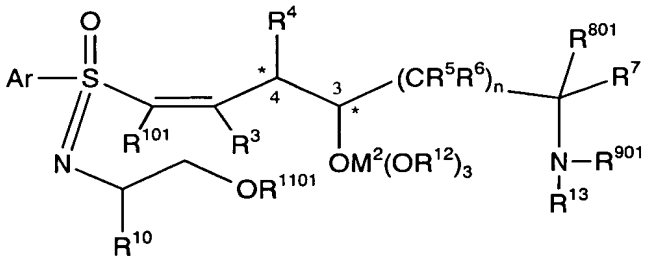
R^5, R^6, R^7 and n have the above meanings,

R^{801} has the meaning of R^8, with any reactive groups, if necessary, being blocked by base-stable protecting groups,

R^{901} is hydrogen or together with R^{801} forms a C_3-C_4-alkylene chain, and

R^{13} is an amino protecting group which when cleaved leaves behind a nitrogen nucleophile,

to form a stereoisomer of a compound corresponding to the formula IX:



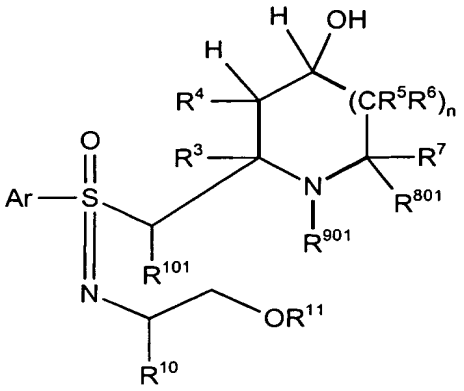
IX

wherein

R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{901}, R^{10}, R^{1101}, R^{12}, R^{13}, n, Ar and M2 have the above meanings,

and

b) converting the compound of Formula IX by treatment with a reagent [suitable] for removing the group R^{13}, into a compound corresponding to formula Xa:



Xa

wherein

R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{901}, R^{10}, n and Ar have the above meanings, and

R^{11} is hydrogen or a silyl protecting group,

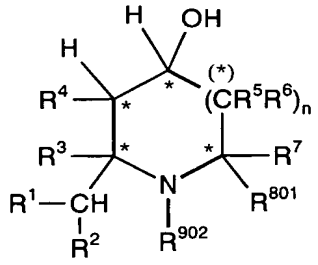
and

if R^{901} is hydrogen, blocking the nitrogen atom in the cyclic parent structure of the resulting compound of Formula Xa with a base-stable protecting group, and

cleaving off any silyl protecting group R^{11} which may still be present;

and

c) for the production of a compound corresponding to formula Ia:



Ia

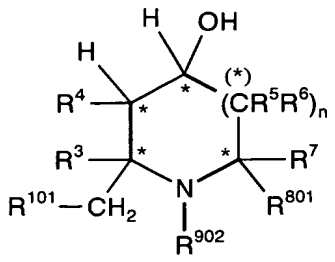
wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{801} and n have the above meanings, and

R^{902} stands for a base-stable protecting group or, together with R^{801}, for a C_3-C_4-alkylene chain,

[ca)] reacting a compound corresponding to formula Xa or a compound produced by cleaving off the silyl protecting group R11 with a reagent

[suitable] for the reductive cleavage of the sulfonimidoyl-alkyl bond, in order to obtain a compound corresponding to formula Ib:

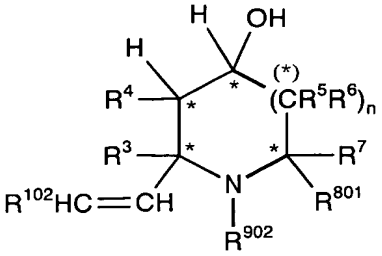


Ib

wherein

R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{902} and n have the above meanings, [or]

[cb) in a resulting compound of Formula Xa wherein R^{101} is other than hydrogen, electrophilically activating the sulfonimidoyl unit and cleaving sulfonimidoyl-alkyl bond under the conditions of a base-induced elimination, in order to obtain a compound corresponding to formula Ic,



Ic

wherein]

[R^3, R^4, R^5, R^6, R^7, R^{801}, R^{902} and n have the above meanings, and]

[R^{102} stands for C_1-C_5-alkyl or for phenyl-lower alkyl optionally substituted one or more times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy, the lower alkylene chain of which phenyl-lower alkyl may contain 1 to 5 carbon atoms,]

and

optionally [if desired,] cleaving off any protecting groups in compounds of Formula Ia,

and

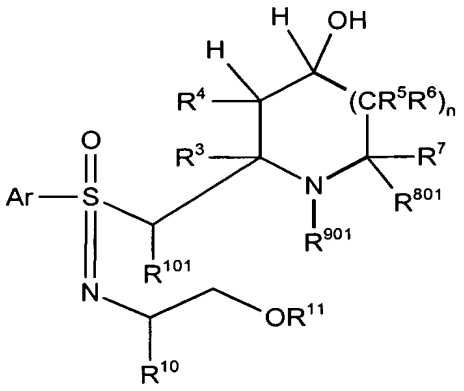
optionally [if desired,] reacting the optionally released NH group in the 1-position of the cyclic parent structure with a reagent capable of N-alkylation or a reagent capable of amide formation or blocking the released NH group with an amino protecting group,

thereby obtaining said compound corresponding to Formula Ia'.

23. (Amended) A process according to claim 17, wherein in step c) [ca)], the sulfonimidoyl-alkyl bond in the compound corresponding to formula Xa is reductively cleaved with samarium (II) iodide.

24. (Amended) A process according to claim 17, wherein R^4 is other than hydrogen in each of the compounds corresponding to formulas Ia', Ia, I b, [Ic,] II, IX and Xa.

27. (Amended) A compound corresponding to formula Xa:



Xa

wherein

n is 0 or 1,

R^3 is hydrogen, and

R^4 is hydrogen[;] or lower alkyl[; or phenyl-lower alkyl optionally substituted one or more times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy], or

R^3 and R^4 also together are a [C_2-alkylene chain; or a] C_3-C_6-alkylene chain optionally containing 1 to 3 double bonds[, which may be bridged by C_1-C_2-alkylene which is optionally substituted one or two times by lower alkyl,] or together form the 7, 7-dimethyl [3.1.1] heptyl-system

R^5 is hydrogen[;] or lower alkyl[; hydroxy; lower alkoxy; phenyl-lower alkoxy or phenyl-lower alkyl each of which may be optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy], and

R^6 is hydrogen, and

R^7 is hydrogen,

R^{10} is lower alkyl, or phenyl optionally substituted once in the phenyl ring by lower alkyl or by hydroxy protected with a suitable protecting group, or phenyl-lower alkyl optionally substituted once in the phenyl ring by lower alkyl,

R^{11} is hydrogen or a silyl protecting group,

R^{101} is hydrogen; [C_1-C_6-alkyl; or phenyl-C_1-C_6-alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

R^{801} is hydrogen;

[cyano;]

[carboxy optionally esterified with cycloaliphatic or straight-chain or branched aliphatic C_1-C_6-alcohols optionally containing one to three double bonds, and optionally substituted one to three times by halogen or lower alkoxy, or alternatively esterified with phenyl-lower alcohols optionally substituted in the phenyl ring one to three times by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[carbonylamino optionally substituted at the nitrogen once by C_3-C_8-cycloalkyl lower alkanoyl or straight-chain or branched aliphatic C_1-C_6-alkanoyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or optionally substituted at the nitrogen once by phenyl-lower alkanoyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy, or optionally substituted at the nitrogen one or two times by C3-C_8-cycloalkyl-lower alkyl or straight-chain or branched aliphatic C_1-C_6-alkyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or by phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[carbonylamino substituted at the nitrogen with a suitable amino protecting group;]

a monocyclic or bicyclic ring system <u>selected from the group consisting of cyclopropyl, cyclopenpyl, cyclohexyl, phenyl, p-biomophenyl and 3-indolyl;</u> [with 3 to 10 ring carbon atoms which is optionally unsaturated one to four times, the ring carbon atoms of said ring system optionally being replaced one to three times by nitrogen, oxygen and/or sulfur and which ring system may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, hydroxy, halogen or by a lower

alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system;]

lower alkyl; phenyl-lower alkyl or lower-alkoxy lower alkyl [a straight-chain or branched C_1-C_{12}-alkyl group optionally containing one to three double bonds, which may optionally be substituted one to three times by]

[halogen,]

[hydroxy,]

[lower alkoxy,]

[carboxy optionally esterified with cycloaliphatic or straight-chain or branched aliphatic C_1-C_6-alcohols, which optionally contain one to three double bonds, and which are optionally substituted one to three times by halogen or lower alkoxy,]

[carboxy esterified with phenyl-lower alcohols optionally substituted in the phenyl ring one to three times by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy;]

[cyano,]

[mercapto,]

[lower alkylthio,]

[amino,]

[lower alkylamino,]

[carbonylamino optionally substituted once at the nitrogen by C_3-C_8-cycloalkyl-lower alkanoyl or straight-chain or branched aliphatic C_1-C_6-alkanoyl, which in each case are optionally substituted one to three times by halogen or lower alkoxy, or optionally substituted once at the nitrogen by phenyl-lower alkanoyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

[carbonylamino substituted once or twice at the nitrogen by C_3-C_8-cycloalkyl-lower alkyl or straight-chain or branched aliphatic C1-C_6-alkyl, which are each optionally substituted one to three times by halogen or lower alkoxy, or by phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy,]

[carbonylamino substituted at the nitrogen with a suitable amino protecting group,]

[a monocyclic or bicyclic ring system with 3 to 10 ring carbon atoms which is optionally unsaturated one to four times, the ring

carbon atoms of which may be replaced one to three times by nitrogen, oxygen and/or sulfur and which ring system may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system, or]

[R^5 and R^{801} also, together with the carbon atoms to which they are bonded, may form a monocyclic or bicyclic ring system with 5 to 10 ring carbon atoms which optionally contains 1 to 3 double bonds, wherein carbon atoms not bearing the substituents R^5 or R^{801} optionally may be replaced one to three times independently by sulfur, oxygen or nitrogen, and which optionally may be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system,] or

R^6 and R^7 also together may form a bond, and

R^5 and R^{801}, together with the carbon atoms to which they are bonded, may form an aromatic C_6-ring system [which may be fused with 2 to 4 further carbon atoms to form a bicyclic ring system having a total of 3 to 5 double bonds which contains a total of 8 to 10 ring carbon atoms, wherein the carbon atoms of this C_6- to C_{10}-ring system which do not bear the substituents R^5 or R^{801} may be replaced one to three times independently by sulfur, oxygen or nitrogen, and wherein this C_6- to C_{10}-ring system may optionally be substituted one to three times by lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, hydroxy, halogen or by a lower alkylene chain which is bonded to two oxygen atoms bonded to adjacent carbon atoms of the ring system,]

[and wherein any reactive groups in R^{801} are blocked by base-stable protecting groups,]

R^{901} is hydrogen or together with R^{801} forms a C_3-C_4-alkylene chain, and

Ar represents phenyl optionally substituted one to three times by lower alkyl,

wherein the sulfur-containing substituent in the 5-position and the hydroxy group in the 3-position of the cyclic parent structure are in the trans position relative to each other, and

wherein the substituent R^4 in the 4-position and the hydroxy group in the 3-position of the cyclic parent structure are in the cis position relative to each other, or

a compound obtainable by removal of any protecting groups which may be present in said compound corresponding to formula Xa, or

an acid addition salt formed with a free amino group which may be present in said compound corresponding to formula Xa.

29. (Amended) A compound according to claim [28] 27, wherein R^{801} and R^{901} together form a C_3-C_4-alkylene chain.